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An efficient catalyst free synthesis of nitrogen containing spiro heterocycles *via* [5 + 1] double Michael addition reaction†

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2,4-Diazaspiro[5.5]undecane-1,3,5,9-tetraones and 3-thioxo-2,4-diazaspiro[5.5]undecane-1,5,9-triones have been synthesized *via* double Michael addition of 1,5-diaryl-1,4-pentadien-3-one with active methylene compounds such as *N*,*N*-dimethyl barbituric acid, barbituric acid, thio-barbituric acid and *N*,*N*-diphenyl thiobarbituric acid in ethylene glycol at 100 °C in the absence of any catalyst to give high yields within a short reaction time. The structure has been confirmed by X-ray analysis. The single-crystal structure of the diazaspiro compound revealed that the C_{Ar}–H···π, π–π stacking and intermolecular hydrogen bonding interactions act as major driving forces for crystal packing.

1. Introduction

Spiro compounds having cyclic structures fused at a central carbon are of recent interest due to their interesting conformational features and their structural importance in biological systems.[1] Nitrogen heterocycles are present in many compounds of practical importance ranging from pharmaceutical agents to biological probes. Diazaspiro[5.5]undecane-1,3,5,9-tetraones and 3-thioxo-2,4-diazaspiro[5.5]undecane-1,5,9-triones show a wide range of biological and therapeutic properties such as antibacterial,[2] potent sedative-hypnotic[3] and CNS depressant properties.[4] They are also known to exhibit anticonvulsant,[5] and fungicidal[6] properties. On the other hand, barbituric acid has been used as a disperse dye with strong fluorescence and as yellow organic pigment.[7–9] In this regard, efficient and facile methodologies for constructing nitrogen containing spiro heterocycles are valuable.

Michael reaction is one of the most versatile processes in organic synthesis.[10–12] The intermolecular double-Michael reactions are particularly powerful tools for assembling complex cyclic products from simple acyclic starting materials. Over the last few decades, a certain number of syntheses in presence of catalyst for compounds containing quaternary carbon center *via* double Michael addition have been reported.[13] In addition there are few reports on the synthesis of diazaspiro[5.5]undecane derivatives despite their importance. Literature survey revealed that the 2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraone and 3-thioxo-2,4-diazaspiro[5.5]undecane-1,5,9-trione derivatives[2–6] have been synthesized by triethanolamine as catalyst in different solvents under reflux. All the reported methods have some limitations, such as long reaction times, limited substrate scope and invoke the application of a catalyst for the synthesis of these biologically active compounds.

Our group has been focusing on development of synthetic methodologies for the synthesis of novel heterocycles.[14] Therefore, we decided to investigate the synthesis of spiro barbiturates and thiobarbiturates using environmentally benign methodologies.

2. Results and discussion

This is the first report of a simple, inexpensive, and fairly efficient catalyst free synthesis of diazaspiro compounds containing barbiturates/thiobarbiturates moieties *via* the double Michael addition of dibenzalacetone derivatives and *N*,*N*-dimethylbarbituric acid/barbituric acid/thiobarbituric acid in ethylene glycol (EG) at 100 °C. We attempted reaction of dibenzylidene acetone (**1a**) and *N*,*N*-dimethyl barbituric acid (**2a**) with different basic catalysts in solvents like ethylene glycol, PEG-400, morpholine and ionic liquids. We obtained the desired 2,4-dimethyl-7,11-diphenyl-2,4-diazaspiro[5.5]-undecane-1,3,5,9-tetraone (**3a**) in varying amounts under different conditions. When we attempted the above reaction in absence of any catalyst for comparison, we realized that a good amount of product (40%) was obtained when the reaction was carried out in ethylene glycol at 50 °C for 24 h. Therefore, we believed that the desired product could be obtained without any catalyst. Subsequently, we carried out the reaction of dibenzylidene acetone (**1a**) and *N*,*N*-dimethyl barbituric acid (**2a**) in ethylene glycol at 60 °C which yielded 52% of product after 12 h, reaction at 80 °C gave 60% of

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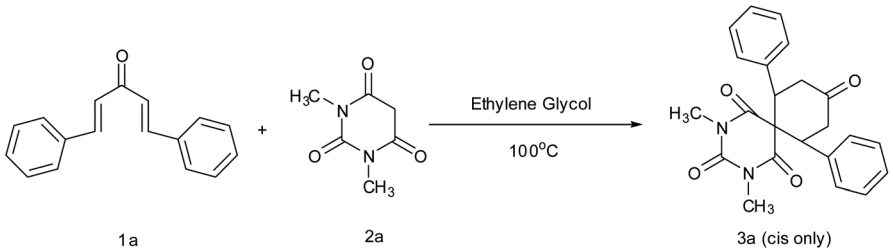
† Electronic supplementary information (ESI) available: Copies of NMR spectra for all compounds. CCDC 951532. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ra00521j

Table 1 Optimization of reaction conditions for double Michael addition reactions[a]



Entry	Solvent	Temperature	Time	Yield (%)
1	EG	50 °C	24 h	40[b]
2	EG	60 °C	12 h	52[b]
3	EG	80 °C	4 h	60[b]
4	EG	100 °C	30 min	91
5	EG	rt	24 h	—[c]
6	EtOH	Reflux	24 h	—[c]
7	MeOH	Reflux	24 h	—[c]
8	Water	Reflux	24 h	—[c]

[a] Reaction conditions: dibenzylidene acetone (1 mmol), *N*,*N*-dimethyl barbituric acid, different solvents, different temperature. [b] Reaction was incomplete. [c] No reaction.

product after 4 h and reaction at 100 °C was complete in 30 min and yielded 91% of the desired product after work up. However, there was no reaction even after 24 h at room temperature (entries 1–5, Table 1). When the reaction was performed in ethanol, methanol or water as solvent under reflux, there was no reaction even after 24 h (Table 1, entries 6–8).

Subsequently reactions of other diarylidene acetones with *N*,*N*-dimethyl barbituric acid in ethylene glycol at 100 °C were also complete in 35–55 min and gave the corresponding 2,4-dimethyl-7,11-diphenyl-2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraone derivatives (**3a–e**, Fig. 1) in good yields. We then attempted the reactions of diarylidene acetones with barbituric acid under same reaction conditions. Expectedly, these substrates also underwent smooth, double Michael addition to give the corresponding spiro derivatives namely 7,11-diphenyl-2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraones in good yields (**3f–j**, Fig. 1).

The scope and generality of the reaction was further examined by replacing barbituric acid with thiobarbituric acid and *N*,*N*-diphenylthiobarbituric acid. All the reactions proceeded smoothly under identical conditions leading to the formation of 7,11-diphenyl-3-thioxo-2,4-diazaspiro[5.5]undecane-1,5,9-triones and 2,4,7,11-tetraphenyl-3-thioxo-2,4-diazaspiro[5.5]undecane-1,5,9-triones in high yields (**5a–j**, Fig. 2). It was also observed that the double Michael addition reaction of diarylidine acetone derivatives with thiobarbituric acid proceeded faster as compared to *N*,*N*-diphenylthiobarbituric acid. All the products were characterized by spectral data.

A plausible mechanism for the formation of diazaspiro derivatives (**3** and **5**) is proposed in Scheme 1. We believe that the presence of the reactive –OH groups in ethylene glycol play a major role[15] in promoting its activity for the formation of enolate form (**4**). This enolate form (**4**) adds to the divinyl ketone (**1**) by intermolecular Michael addition reaction to produce intermediate (**6**). The next step involves the intramolecular Michael addition reaction of the intermediate enolate form (**7**) to the vinyl ketone component of the molecule in such a manner that the more stable product with aryl groups in the equatorial position is formed thus leading to high stereoselectivity (**3** and **5**).

The formation of the product **3b** was confirmed through spectral analysis, as shown in Fig. 3. The ^{1}H NMR spectrum of **3b**, exhibited one doublet of doublet for H3 and H5 protons at 3.92 δ with $J = 14.3$ Hz and 4.4 Hz. The CH_2 protons of C2 and C6 positions appeared as one doublet of doublet of $H2_{(e)}$ and $H6_{(e)}$ at 2.53 δ with $J = 15.02$ Hz and 4.4 Hz and one triplet of $H2_{(a)}$ and $H6_{(a)}$ at 3.63 δ with 14.6 Hz. Furthermore, the structure of **3b** was also determined by the single crystal X-ray crystallography. Single crystals suitable for X-ray diffraction were grown by vapour diffusion of hexane into chloroform solution of **3b** at room temperature. X-ray diffraction structure of **3b** is shown in Fig. 4.

X-ray crystal structure analysis of **3b** confirms the preferred *cis* configuration of the cyclohexanone ring with regard to the two substituted phenyl rings and also the presence of a plane of symmetry in a molecule. For compound **3b**, the chair like conformation is strongly preferred, because both the substituted phenyl rings can be accommodated in equatorial positions (Fig. 5).

In X-ray analysis of compound **3b**, there are some intramolecular interactions between the phenyl ring and the nitrogen atoms of barbituric acid ring (C_{Ar}–H···N–CH_3), with the distance 3.15–3.44 Å (Fig. 6). The structure also involves weak intermolecular π–π aromatic stacking interactions between centroids of the π-rings with a centroid–centroid

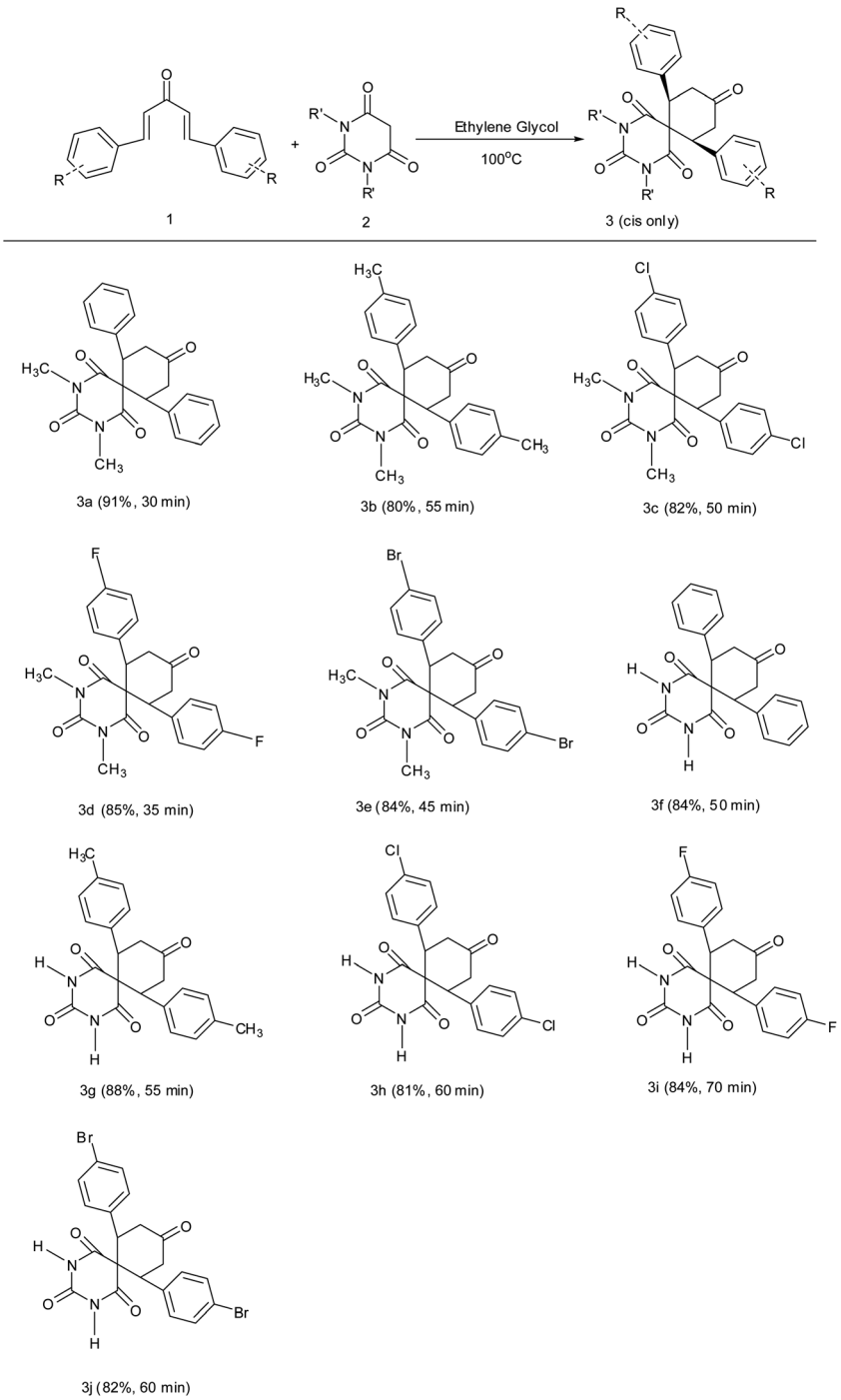


Fig. 1 Double Michael addition of diarylidene acetone derivatives with barbituric acid and *N,N*-dimethyl barbituric acid in ethylene glycol at 100 °C.

distance of 5.028–7.774 Å and the angle between the planes of two π-rings approaching 90° as shown in Fig. 7. Moreover, weak attractive C–H···π interactions between the hydrogen of phenyl ring and centroid of the phenyl ring, with a distance of 3.329 and 4.568 Å are also observed. This indicates that the aromatic–aromatic stabilization is perhaps more due to C–H···π type of interactions rather than π–π stacking interactions.

Besides the π–π stacking and the C–H···π interactions, intermolecular hydrogen bonding interactions also play vital role to stabilize the packing of the molecule. In the packing diagram (Fig. 7) the molecules are linked through the intermolecular hydrogen bonding interactions between the C_{Ar}–H···O with bond distance of 2.715–3.111 Å. Donor–accepter bond distances suggest that the hydrogen atom of the phenyl ring is expected to involve in hydrogen-bonding with the oxygen atoms of cyclohexanone and barbituric acid rings. The distances of the donor–H, acceptor···H, donor···acceptor and donor–H···acceptor angles are presented in Table 2.

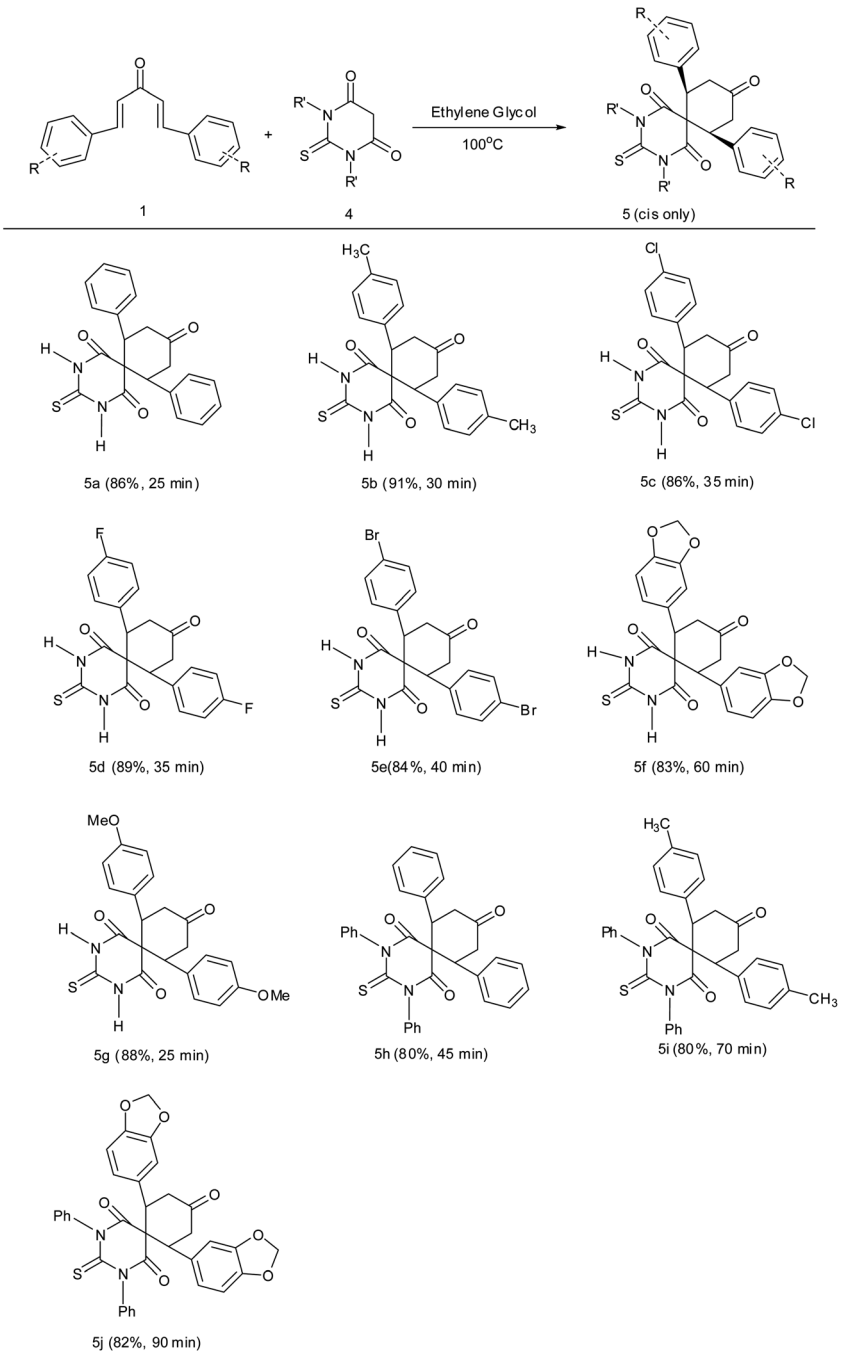


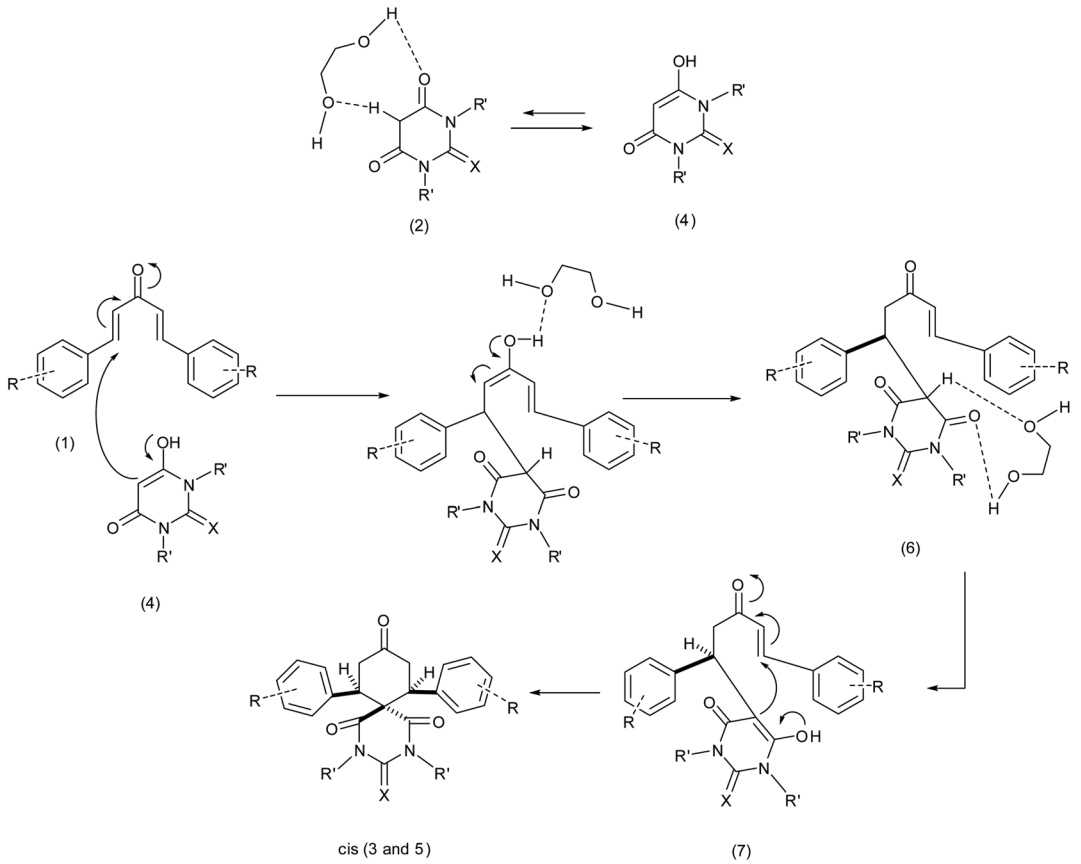
Fig. 2 Double Michael addition of diarylidene acetones with thiobarbituric acid and *N*,*N*-diphenyl thiobarbituric acid in ethylene glycol at 100 °C.

3. Conclusion

In conclusion, we have reported a highly efficient, catalyst free synthesis of diazaspiro compounds *via* intermolecular and intramolecular double Michael addition reaction using ethylene glycol as an inexpensive and commercially available media. This method not only offers substantial improvements in the reaction rates, yields and also avoids the use of hazardous catalyst. We also examined the crystal structure and packing of diazaspiro compound.

4. Experimental

All the starting materials were of GR quality of Merck and all solvents used were of HPLC grade. Melting points were determined on a Tropical Lab equip apparatus and are uncorrected. IR (KBr) spectra were recorded on Perkin-Elmer FTIR spectrophotometer and the values are expressed as ν_{max} cm^{-1}. Mass spectral data were recorded on Agilent 6520 Q-Tof (ESI-HRMS) mass spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Jeol JNM ECX-400P at 400 MHz and 100 MHz,



Scheme 1 Plausible mechanism for the synthesis of diazaspiro compounds in ethylene glycol.

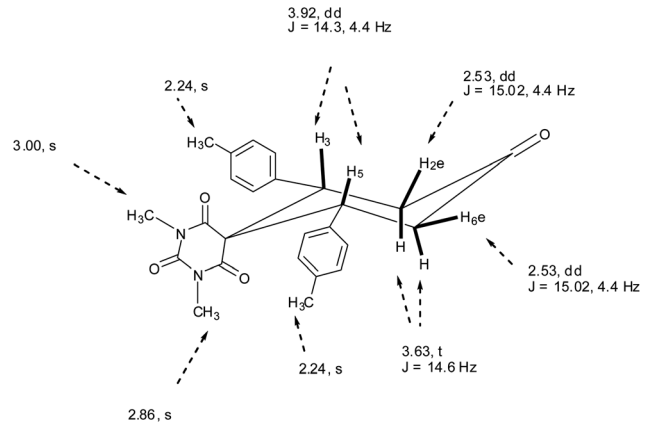


Fig. 3 ^{1}H NMR of **3b**.

respectively using TMS as an internal standard. The chemical shift values are recorded on δ scale and the coupling constants (J) are in hertz. X-ray intensity data were collected on an Oxford Diffraction Xcalibur CCD diffractometer with graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) at 298 K. The data was collected at 293 K and the structures were resolved by direct methods and refined by full-matrix least-squares on F^2 (SHELXL-97).[16] All calculations were carried out using the WinGX package of the crystallographic programs.†[17]

4.1. General procedure for the synthesis of diazaspiro compounds

In a general procedure, diarylidene acetone (1 mmol), *N*,*N*-dimethyl barbituric acid/barbituric acid/thiobarbituric acid/*N*,*N*-diphenyl thiobarbituric acid (1 mmol) and 2 mL of ethylene glycol were taken in a 50 mL round bottomed flask. The reaction mixture was heated in an oil-bath maintained at 100 °C and the progress of the reaction was monitored by TLC using ethyl acetate–petroleum ether (30 : 70) as eluent for disappearance of diarylidene acetone. After completion of the reaction (Fig. 1 and 2), the reaction mixture was allowed to cool to room temperature and water (2 mL) was added dropwise with stirring. The solid was filtered at pump and washed with water. The product was recrystallized from ethanol. The products were identified by their spectral data.

4.2. Spectral data

4.2.1. 2,4-Dimethyl-7,11-diphenyl-2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraone (3a).[19] White solid, yield: 91%, mp 150–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.59, 2.63 (dd, 2H, $J = 14.6$ Hz, 4.4 Hz), 2.86 (s, 3H, –NCH_3), 3.01 (s, 3H, –NCH_3), 3.69 (t, 2H, $J = 14.6$ Hz), 3.99, 4.03 (dd, 2H, $J = 13.9$ Hz, 4.4 Hz), 7.05–7.07 (m, 4H, Ar-H), 7.23–7.26 (m, 6H, Ar-H).

4.2.2. 2,4-Dimethyl-7,11-di(4-methylphenyl)-2,4-diazaspiro-[5.5]undecane-1,3,5,9-tetraone (3b). White solid, yield: 80%, mp

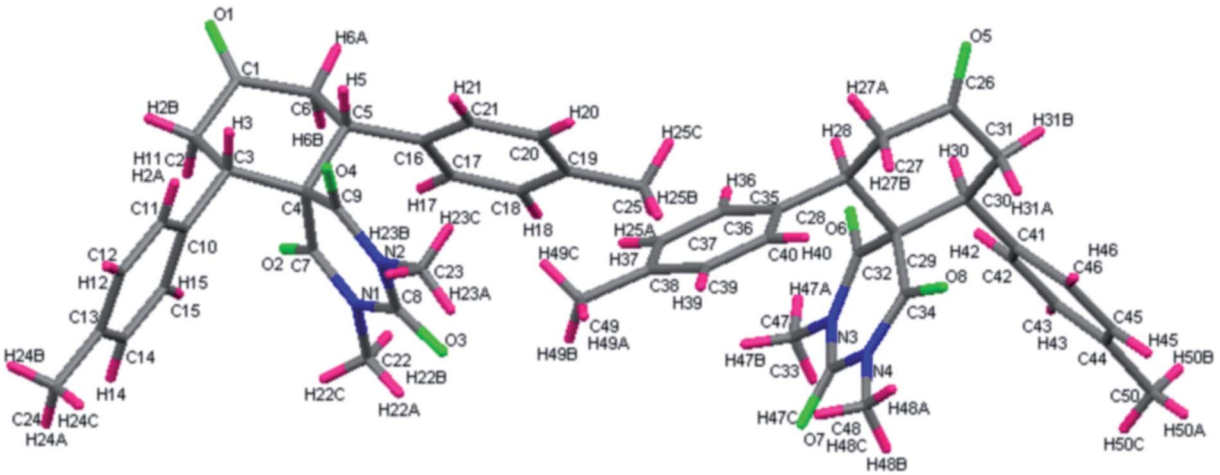


Fig. 4 X-ray crystal structure of **3b**.†

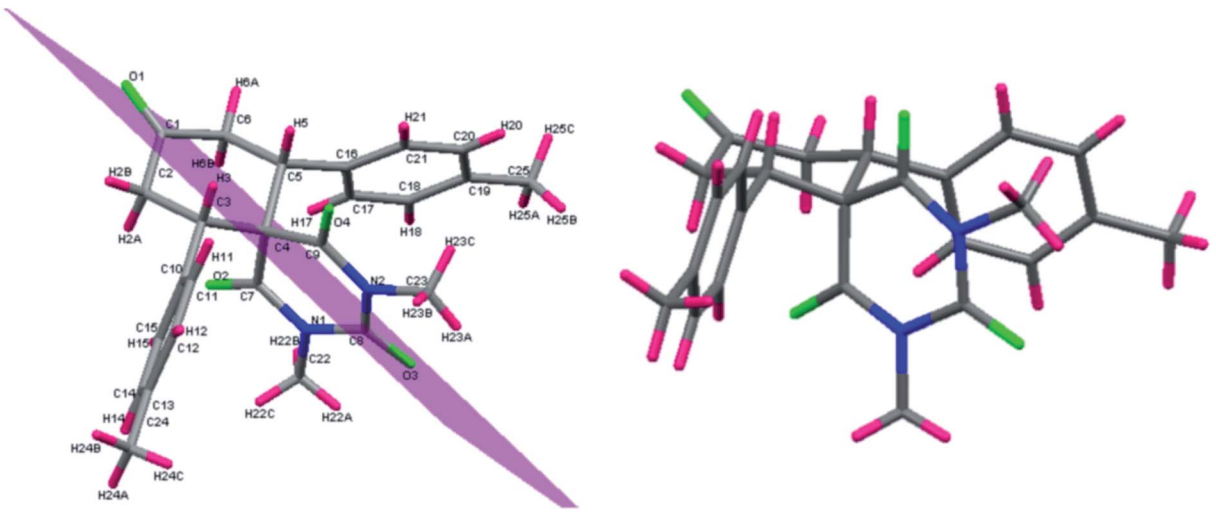


Fig. 5 X-ray crystallographic structure of compound **3b** with indication of the plane of symmetry.

159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.24 (s, 6H, $ArCH_3$), 2.53, 2.57 (dd, 2H, J = 15.02 Hz, 4.4 Hz), 2.86 (s, 3H, $-NCH_3$), 3.00 (s, 3H, $-NCH_3$), 3.63 (t, 2H, J = 14.6 Hz), 3.92, 3.97 (dd, 2H, J = 14.3 Hz, 4.4 Hz), 6.91 (d, 4H, Ar-H, J = 8.0 Hz), 7.00 (d, 4H, Ar-H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.03, 28.45, 30.92, 42.77, 49.75, 60.46, 128.82, 129.13, 134.61, 135.39, 149.30, 168.53, 170.33, 207.14; IR (KBr, cm^{-1}) ν_{max} = 2922, 1781, 1676, 1423, 1379, 1125, 819, 806; HRMS (ESI) m/z [M^+ + H] calculated for $C_{25}H_{27}N_2O_4$ 419.1971, found 419.1963.

4.2.3. 7,11-Bis(4-chlorophenyl)-2,4-dimethyl-2,4-diazaspiro-[5.5]undecane-1,3,5,9-tetraone (3c). White solid, yield: 82%, mp 225 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.53, 2.57 (dd, 2H, J = 14.6 Hz, 4.4 Hz), 2.85 (s, 3H, $-NCH_3$), 3.00 (s, 3H, $-NCH_3$), 3.67 (t, 2H, J = 14.6 Hz), 3.92, 3.96 (dd, 2H, J = 13.9 Hz, 4.4 Hz), 6.91 (d, 4H, Ar-H, J = 8.0 Hz), 7.00 (d, 4H, Ar-H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.85, 28.27, 43.02, 50.07, 60.96, 127.27, 129.45, 134.05, 138.27, 149.79, 169.05, 170.77, 208.56; IR (KBr, cm^{-1}) ν_{max} = 2956, 2925, 1718, 1676, 1449, 1423, 1379, 1284, 1124, 754;

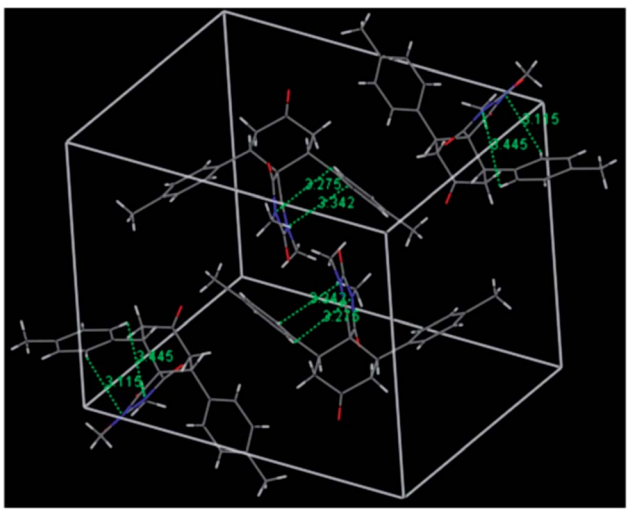


Fig. 6 Intramolecular hydrogen bonding interactions in the crystal packing along b-axis of **3b**.

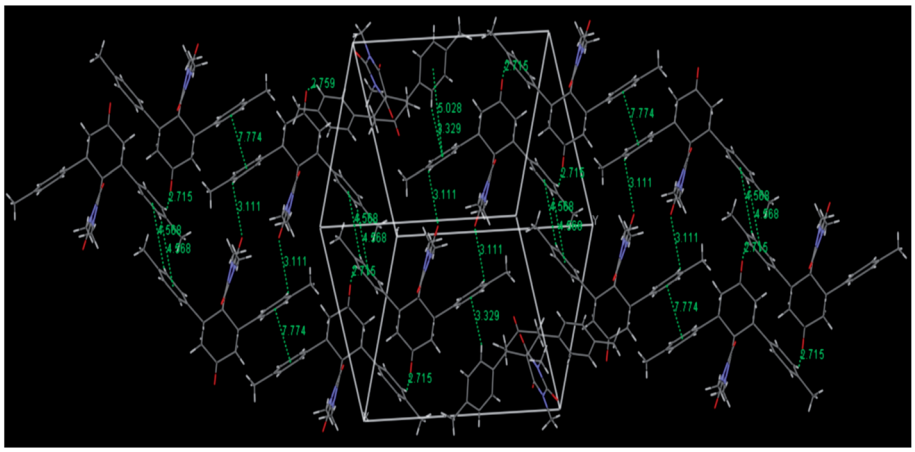


Fig. 7 Intermolecular hydrogen bonding interactions, π···π stacking and C–H···π interactions in the crystal of **3b**.

Table 2 Intermolecular and intramolecular hydrogen bonding geometries of the **3b**[a] (Å, °)

D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)
C45–H45···O5^{i}	1.212	2.715	3.301	108.17
C37–H37···O7^{ii}	0.931	3.111	3.637	117.63
C21–H21···N2^{iii}	0.930	3.445	3.391	85.5
C36–H36···N3^{iv}	0.931	3.275	3.385	88.7
C40–H40···N4^{iv}	0.930	3.342	3.315	80.4

[a] Note: D, donor; A, acceptor. Symmetry codes: (i) $-1+x, -1+y, z$; (ii) $2-x, 3-y, 2-z$; (iii) x, y, z; (iv) $2-x, 2-y, 1-z$.

HRMS (ESI) m/z [M^+ + H] calculated for $C_{23}H_{21}Cl_2N_2O_4$ 459.0878, found 459.0869.

4.2.4. 7,11-Bis(4-fluorophenyl)-2,4-dimethyl-2,4-diazaspiro-[5.5]undecane-1,3,5,9-tetraone (3d). White solid, yield: 85%, mp 154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.55, 2.59 (dd, 2H, J = 14.6 Hz, 4.4 Hz), 2.88 (s, 3H, –NCH_3), 3.02 (s, 3H, –NCH_3), 3.64 (t, 2H, J = 14.6 Hz), 3.95, 3.96 (dd, 2H, J = 13.9 Hz, 4.4 Hz), 6.91 (d, 4H, Ar-H, J = 8.0 Hz), 7.00 (d, 4H, Ar-H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.96, 28.39, 42.97, 49.57, 60.85, 115.89 (d, J^2 = 21.9 Hz), 129.16 (d, J^3 = 8.6 Hz), 132.78 (d, J^4 = 2.9 Hz), 149.32, 162.43 (d, J^1 = 239 Hz), 168.78, 170.51, 207.42; IR (KBr, cm^{-1}) ν_{max} = 3049, 2927, 1719, 1675, 1510, 1424, 1226, 1162, 835; HRMS (ESI) m/z [M^+ + H] calculated for $C_{23}H_{21}F_2N_2O_4$ 427.1469, found 427.1460.

4.2.5. 7,11-Bis(4-bromophenyl)-2,4-dimethyl-2,4-diazaspiro-[5.5]undecane-1,3,5,9-tetraone (3e). White solid, yield: 84%, mp 215 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.53 (dd, 2H, J = 14.6 Hz, 4.1 Hz), 2.88 (s, 3H, –NCH_3), 3.03 (s, 3H, –NCH_3), 3.59 (t, 2H, J = 14.6 Hz), 3.92 (dd, 2H, J = 14.2 Hz, 4.5 Hz), 6.91 (d, 4H, Ar-H, J = 8.6 Hz), 7.35 (d, 4H, Ar-H, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.04, 28.67, 42.70, 49.92, 60.29, 122.79, 128.99, 129.26, 131.96, 132.23, 135.90, 149.11, 168.43, 170.20, 207.10; IR (KBr, cm^{-1}) ν_{max} = 2925, 1710, 1680, 1420, 1378, 1283, 1075, 829; HRMS (ESI) m/z [M^+ + H] calculated for $C_{23}H_{21}Br_2N_2O_4$ 548.9848, found 548.9829.

4.2.6. 7,11-Diphenyl-2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraone (3f).[6] White solid, yield: 84%, mp 275–277 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 2.44, 2.48 (dd, 2H, J = 15.4 Hz, 4.4 Hz), 3.49 (t, 2H, J = 14.6 Hz), 3.96, 3.99 (dd, 2H, J = 14.3 Hz, 4.4 Hz), 7.13 (d, 4H, Ar-H, J = 7.3 Hz), 7.27–7.34 (m, 6H, Ar-H), 11.20 (s, 1H, –NH), 11.46 (S, 1H, –NH).

4.2.7. 7,11-Di(4-methylphenyl)-2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraone (3g).[20] White solid, yield: 88%, mp 266–268 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 2.26 (s, 3H, –$ArCH_3$), 2.56, 2.59 (dd, 2H, J = 15.4 Hz, 4.4 Hz), 3.62 (t, 2H, J = 14.6 Hz), 3.90, 3.94 (dd, 2H, J = 13.9 Hz, 4.4 Hz), 6.99–7.05 (m, 8H, Ar-H), 7.67 (s, 1H, –NH), 7.83 (s, 1H, –NH).

4.2.8. 7,11-Bis(4-chlorophenyl)-2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraone (3h).[6] White solid, yield: 81%, mp 238–240 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.57, 2.61 (dd, 2H, J = 14.7 Hz, 4.4 Hz), 3.58 (t, 2H, J = 14.6 Hz), 3.92, 3.95 (dd, 2H, J = 13.9 Hz, 4.4 Hz), 7.07 (d, 4H, Ar-H, J = 8.1 Hz), 7.25 (d, 4H, Ar-H, J = 8.8 Hz), 7.98 (s, 1H, –NH), 8.14 (s, 1H, –NH).

4.2.9. 7,11-Bis(4-fluorophenyl)-2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraone (3i). Pale yellow solid, yield: 84%, mp 137 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.73 (dd, 2H, J = 12.46 Hz, 2.96 Hz), 2.77 (t, 2H, J = 13.28 Hz), 3.74 (dd, 2H, J = 13.9 Hz, 3.6 Hz), 7.06–7.16 (m, 8H, Ar-H), 11.18 (s, 1H, –NH), 11.24 (s, 1H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 35.60, 46.86, 63.92, 115.49 (d, J^2 = 22.9 Hz), 129.89 (d, J^3 = 7.6 Hz), 134.59 (d, J^4 = 2.9 Hz), 148.85, 161.51 (d, J^1 = 243.1 Hz), 170.34, 172.78, 206.54; IR (KBr, cm^{-1}) ν_{max} = 3221, 2926, 2854, 1714, 1509, 1364, 1227, 1161, 1078; HRMS (ESI) m/z [M^+ + H] calculated for $C_{21}H_{17}F_2N_2O_4$ 399.1156, found 399.1150.

4.2.10. 7,11-Bis(4-bromophenyl)-2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraone (3j). Creamish solid, yield: 82%, mp 139 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.42–2.46 (m, 1H), 2.64–2.82 (m, 1H), 3.46–3.51 (m, 1H), 3.69–3.75 (m, 1H), 3.92–3.99 (m, 2H), 6.98–7.05 (m, 4H, Ar-H), 7.47–7.53 (m, 4H, Ar-H), 11.33 (s, 1H, –NH), 11.55 (s, 1H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 42.32, 48.04, 64.07, 121.38, 130.02, 131.76, 136.81, 148.75, 170.49, 171.57, 206.54; IR (KBr, cm^{-1}) ν_{max} = 3220, 2926, 2854, 1712, 1375, 1217, 1075; HRMS (ESI) m/z [M^+ + H] calculated for $C_{21}H_{17}Br_2N_2O_4$ 520.9535, found 520.9527.

4.2.11. 7,11-Diphenyl-3-thioxo-2,4-diazaspiro[5.5]undecane-1,5,9-trione (5a).[18] White solid, yield: 86%, mp 254–256 °C; ^{1}H

NMR (400 MHz, $CDCl_3$) δ: 2.62, 2.66 (dd, 2H, J = 15.4 Hz, 4.4 Hz), 3.64 (t, 2H, J = 15.4 Hz), 3.95, 3.99 (dd, 2H, J = 14.7 Hz, 4.4 Hz), 7.12–7.15 (m, 4H, Ar-H), 7.27–7.28 (m, 6H, Ar-H), 8.35 (s, 1H, –NH), 8.55 (S, 1H, –NH).

4.2.12. 3-Thioxo-7,11-di(4-methylphenyl)-2,4-diazaspiro[5.5]-undecane-1,5,9-trione (5b).[18] Pale yellow solid, yield: 91%, mp 236–238 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.84, 1.88 (dd, 2H, J = 13.2 Hz, 2.9 Hz), 2.24 (s, 3H, –$ArCH_3$), 2.91 (t, 2H, J = 13.6 Hz), 3.89, 3.93 (dd, 2H, J = 13.5 Hz, 3.7 Hz), 6.99–7.04 (m, 8H, Ar-H), 8.30 (s, 1H, –NH), 8.32 (S, 1H, –NH).

4.2.13. 7,11-Bis(4-chlorophenyl)-3-thioxo-2,4-diazaspiro[5.5]-undecane-1,5,9-trione (5c).[2] Pale yellow solid, yield: 86%, mp 238–240 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.83, 1.86 (dd, 2H, J = 12.8 Hz, 3.7 Hz), 2.87 (t, 2H, J = 13.6 Hz), 3.90, 3.94 (dd, 2H, J = 13.5 Hz, 3.7 Hz), 7.05 (d, 4H, Ar-H, J = 8.8 Hz), 7.20 (d, 4H, Ar-H, J = 8.4 Hz), 8.69 (s, 1H, –NH), 8.73 (S, 1H, –NH).

4.2.14. 7,11-Bis(4-fluorophenyl)-3-thioxo-2,4-diazaspiro[5.5]-undecane-1,5,9-trione (5d). Dirty white solid, yield: 89%, mp 246–248 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.75, 1.78 (dd, 2H, J = 12.8, 3.68 Hz), 2.78 (t, 2H, J = 13.56 Hz), 3.75, 3.79 (dd, 2H, J = 13.56, 3.68 Hz), 7.02–7.12 (m, 8H, Ar-H), 12.21 (s, 1H, –NH), 12.24 (s, 1H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 35.85, 47.02, 60.12, 115.51 (d, J^2 = 21.0 Hz), 129.89 (d, J^3 = 7.6 Hz), 134.54 (d, J^4 = 2.9 Hz), 161.5 (d, J^1 = 243.1 Hz), 167.92, 170.62, 177.60, 203.97; IR (KBr, cm^{-1}) ν_{max} = 3221, 2925, 1690, 1512, 1327, 1229, 1164, 841; HRMS (ESI) m/z [M^+ + H] calculated for $C_{21}H_{17}F_2N_2O_3S$ 415.0928, found 415.0551.

4.2.15. 7,11-Bis(4-bromophenyl)-3-thioxo-2,4-diazaspiro[5.5]-undecane-1,5,9-trione (5e). Pale yellow solid, yield: 84%, mp 250–252 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.43–2.44 (m, 1H), 2.63–2.85 (m, 2H), 3.85–3.07 (m, 1H), 3.71–3.77 (m, 1H), 3.93–4.01 (m, 2H), 6.98–7.05 (m, 4H, Ar-H), 7.46–7.51 (m, 4H, Ar-H), 12.22–12.29 (b, 2H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 35.58, 47.37, 64.03, 120.95, 130.13, 131.73, 137.57, 167.89, 170.94, 177.63, 206.17; IR (KBr, cm^{-1}) ν_{max} = 3186, 2925, 1700, 1524, 1369, 1321, 1216, 1151, 1073; HRMS (ESI) m/z [M^+ + H] calculated for $C_{21}H_{17}Br_2N_2O_3S$ 536.9306, found 536.9292.

4.2.16. 7,11-Di(benzo[*d*][1,3]dioxol-5-yl)-3-thioxo-2,4-diazaspiro[5.5]undecane-1,5,9-trione (5f). Pale yellow solid, yield: 83%, mp 256–258 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.67, 1.70 (dd, 2H, J = 12.8 Hz, 3.7 Hz), 2.66 (t, 2H, J = 13.2 Hz), 3.62, 3.65 (dd, 2H, J = 13.5 Hz, 3.7 Hz), 5.92 (s, 4H, –OCH_2O–), 6.47–6.50 (m, 4H, Ar-H) 6.77 (d, 2H, Ar-H, J = 8.0 Hz), 12.19 (bs, 2H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 36.19, 47.66, 64.02, 101.06, 107.88, 108.38, 121.43, 131.83, 146.42, 147.41, 168.27, 170.85, 177.58, 206.48; IR (KBr, cm^{-1}) ν_{max} = 3206, 2900, 1727, 1686, 1520, 1488, 1355, 1315, 1242, 1159, 1040, 824; HRMS (ESI) m/z [M^+ − H] calculated for $C_{23}H_{17}N_2O_7S$ 465.0756, found 465.0768.

4.2.17. 7,11-Bis(4-methoxyphenyl)-3-thioxo-2,4-diazaspiro-[5.5]undecane-1,5,9-trione (5g).[2] Yellow solid, yield: 88%, mp 207–209 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.83, 1.86 (dd, 2H, J = 12.8 Hz, 3.7 Hz), 2.88 (t, 2H, J = 13.6 Hz), 3.72 (s, 6H, –OCH_3), 3.87, 3.91 (dd, 2H, J = 13.9 Hz, 3.7 Hz), 6.73 (d, 4H, J = 8.8 Hz), 7.04 (d, 4H, J = 8.8 Hz), 8.51 (s, 1H, –NH), 8.54 (s, 1H, –NH).

4.2.18. 2,4,7,11-Tetraphenyl-3-thioxo-2,4-diazaspiro[5.5]-undecane-1,5,9-trione (5h).[18] Pale yellow solid, yield: 80%, mp 248–250 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.68 (d, 2H, J = 13.9 Hz), 3.71 (t, 2H, J = 13.9 Hz), 4.18 (d, 2H, J = 13.2 Hz), 6.52 (s, 2H, Ar-H), 6.82 (s, 2H, Ar-H), 7.31–7.46 (m, 16H, Ar-H).

4.2.19. 2,4-Diphenyl-3-thioxo-7,11-dip-tolyl-2,4-diazaspiro[5.5]-undecane-1,5,9-trione (5i).[17] Yellow solid, yield: 80%, mp 238–240 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.80 (d, 1H, J = 13.6 Hz), 2.33 (d, 6H, –$ArCH_3$, J = 10.9 Hz), 2.53–2.57 (m, 1H), 2.90 (t, 1H, J = 13.9 Hz), 3.60 (t, 1H, J = 14.6 Hz), 3.92 (s, 1H), 4.02–4.07 (m, 1H), 6.47 (d, 1H, J = 4.4 Hz, Ar-H), 6.58–6.65 (m, 1H, Ar-H), 6.75 (d, 1H, J = 7.3 Hz, Ar-H), 6.95–6.99 (m, 1H, Ar-H), 7.10–7.21 (m, 7H, Ar-H), 7.32–7.46 (m, 6H, Ar-H), 7.62–7.66 (m, 1H, Ar-H).

4.2.20. 7,11-Di(benzo[*d*][1,3]dioxol-5-yl)-2,4-diphenyl-3-thioxo-2,4-diazaspiro[5.5]undecane-1,5,9-trione (5j). Yellow solid, yield: 82%, mp 215 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.57, 2.61 (dd, 2H, J = 15.3 Hz, 4.4 Hz), 3.56 (t, 2H, J = 14.6 Hz), 3.98–4.06 (m, 2H), 6.00 (s, 2H, –CH_2), 6.02 (d, 2H, J = 5.12 Hz), 6.60–6.62 (m, 1H, Ar-H), 6.70–6.72 (m, 2H, Ar-H), 6.75–6.76 (m, 2H, Ar-H), 6.81–6.89 (m, 4H, Ar-H), 7.06–7.11 (m, 1H, Ar-H), 7.37–7.49 (m, 6H, Ar-H), 7.60 (s, 1H, Ar-H), 7.64 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 43.18, 50.64, 61.89, 101.59, 106.56, 108.13, 108.63, 121.99, 123.70, 125.05, 127.99, 128.05, 128.91, 129.03, 129.47, 129.66, 130.57, 138.53, 142.87, 147.98, 148.31, 167.76, 169.45, 178.61, 207.68; IR (KBr, cm^{-1}) ν_{max} = 3074, 2905, 1718, 1692, 1645, 1499, 1490, 1362, 1326, 1256, 1037, 930; HRMS (ESI) m/z [M^+ + H] calculated for $C_{35}H_{27}N_2O_7S$ 619.1539, found 619.1526.

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